Effectiveness of hypnosis in third molar extraction: A randomized controlled trial (HypMol)

Running head: HypMol

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Conflict of interest statement

Dr. Meyenberger provides training in hypnotherapy, but no direct financial gains from this study can be expected. All other authors have no conflicting or competing interests to declare.

Significance:

Hypnosis is used as a treatment to reduce pain in general and dental settings. In this study, additional hypnosis with reduced preoperative local anesthetic use did not generally reduce posttreatment pain after third molar extraction more than regular local anesthetics. The expectation of the patients about the effectiveness of hypnosis affected the effectiveness of the hypnosis so that patients with high expectations had a larger benefit from hypnosis than patients with low expectations.

Abstract

Background: Third molar extraction is a painful treatment for patients, and thus, it can be used to investigate the effects of analgesics on pain. Hypnosis can help to reduce pain and to decrease the intake of postoperative systemic analgesics. In this study, the effectiveness of hypnosis for patients undergoing third molar extractions was investigated.

Methods: Data were collected from 33 patients with third molar extractions on the right and left sides. Patients received two different types of pain interventions in this monocentric randomized crossover trial. Third molar extraction was conducted on one side with reduced preoperative local anesthetics and additional hypnosis (Dave Elman technique). The other side was conducted with regular preoperative local anesthetics without hypnosis. Intake of postoperative systemic analgesics was allowed in both treatments. Patients' expectations about hypnosis were assessed at baseline. The primary outcome was the area under the curve with respect to ground (AUC_G) of pain intensity after the treatment. Secondary outcomes were the amount of postoperative analgesics consumed and the preferred treatment.

Results: There was no evidence that the AUC_G of pain differed between the two interventions (controlling for gender), but the patients' expectations affected the effectiveness of hypnosis. This means that patients with high expectations about hypnosis benefit more from treatment with reduced preoperative local anesthetics and additional hypnosis, while there was no evidence that it is likely that patients with low expectations benefit from such a treatment.

Keywords: dental pain; hypnosis; surgery; expectations; clinical trial

Introduction

Third molar extraction is a painful treatment for patients (Benediktsdóttir, Wenzel, Petersen, & Hintze, 2004; Haug, Perrott, Gonzalez, & Talwar, 2005; Lago-Méndez et al., 2007; Mansuri, Mujeeb, Hussain, & Hussain, 2014; Mobilio, Vecchiatini, Vasquez, Calura, & Catapano, 2017; Sato, Asprino, de Araújo, & de Moraes, 2009; Wong, Leung, & Cheung, 2019). Therefore, it can serve as a paradigm for investigating the analgesic effects of different pain treatments. For the medical treatment of pain during third molar extraction, infiltrative and/or conductive anesthesia with local anesthetics is used to reduce the pain to a very low level (Al-Shayyab & Baqain, 2018; Gujer, Jacobsen, & Grätz, 2013; Kim, Hwang, & Park, 2018; Sierra Rebolledo, Delgado Molina, Berini Aytés, & Gay Escoda, 2007). Local anesthetics lose their effectiveness on pain 1 to 3 hours after surgery; therefore, patients should treat their posttreatment moderate-to-severe pain with nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid or ibuprofen (Moll, Derry, Moore, & McQuay, 2011; Moore, Derry, Aldington, & Wiffen, 2015; Ostenfeld et al., 2011; Rowe, Cudmore, & Turner, 1981; Weiser, Richter, Hegewisch, Muse, & Lange, 2018). Additionally, the use of cooling packs to reduce pain or swelling is beneficial (Forouzanfar, Sabelis, Ausems, Baart, & Van Der Waal, 2008; Gujer et al., 2013; Laureano Filho, de Oliveira e Silva, Camargo, & Gouveia, 2005).

Some studies have investigated the effectiveness of hypnosis in third molar extraction. Hypnosis has been reported to be effective in reducing pain and mental distress during and after third molar extraction, in general surgery and in chronic pain conditions (Castel, Pérez, Sala, Padrol, & Rull, 2007; Derbyshire, Whalley, & Oakley, 2009; Gay, Philippot, & Luminet, 2002; Hammond, 2008; Montgomery, David, Winkel, Silverstein, & Bovbjerg, 2002; Tan et al., 2015; Tefikow et al., 2013; Zech, Hansen, Bernardy, & Häuser, 2017). Patients who received hypnosis during third molar extraction reported less pain during the

extraction and during the follow-up compared to patients without hypnosis (Abdeshahi, Hashemipour, Mesgarzadeh, Shahidi Payam, & Halaj Monfared, 2013; Mackey, 2009, 2018; Peimani, Irannezhad, & Ahmadi, 2017). It has also been shown that the postoperative consumption of NSAIDs was reduced when hypnosis was used (Abdeshahi et al., 2013; Enqvist & Fischer, 1997; Mackey, 2009, 2018). Despite the fact that some trials were previously conducted using hypnosis for third molar extraction, their study quality was rather low due to inappropriate allocation of patients, small samples, and a high risk of detection bias since completer analysis was used (see also the discussion section for more details). Recent meta-analyses concluded that hypnosis is effective and common in dental settings (Burghardt, Koranyi, Magnucki, Strauss, & Rosendahl, 2018; Venkiteswaran & Tandon, 2021), but no specification of third molar extraction was done.

A closer inspection of earlier hypnosis studies in third molar extraction showed methodological weaknesses and wide variations in pain ratings among the patients. This study therefore used a within-subject crossover design to balance differences in pain sensitivity within one patient. A within-subject design also has strong advantages with respect to statistical power; since it can be assumed that within-patient correlations of pain are high, this design reduces error in the effect estimates of an intervention if within-subject consistency and between-subject heterogeneity is incorporated into the study design (Cousineau, 2005).

It is unclear whether hypnosis can be delivered to all patients equally or if some patients are more susceptible to hypnotic interventions. The hypnotic susceptibility of patients might alter the treatment effects, but this parameter is difficult to assess since long interviews have to be conducted or pretests within hypnotic inductions need to be applied (Weizenhoffer & Hilgard, 1959). In clinical settings, such detailed interviews are often not feasible, and the reliability between interviewers is questionable (Kirsch, 1997). Previous randomized controlled trials (RCTs) assigned patients to hypnosis irrespective of their hypnotic susceptibility.

Nevertheless, many of these RCTs have shown the effectiveness of hypnosis (Burghardt et al., 2018; Enqvist & Fischer, 1997; Facco et al., 2011; Ghoneim, Block, Sarasin, Davis, & Marchman, 2000; Mackey, 2009). As a proxy measure, the patients' expectations toward hypnosis might reflect hypnotic susceptibility as well as the hypnotic depth during treatment (Brown, Antonova, Langley, & Oakley, 2001; Council, Kirsch, & Hafner, 1986; Pekala et al., 2010).

The aim of this study was to investigate the effectiveness of hypnosis by applying reduced preoperative local anesthetics and additional hypnosis in patients undergoing third molar extraction on both sides with regard to pain and pain medication use compared to regular local anesthetic treatment for this condition. We assessed patients' expectations about the effectiveness of hypnosis before treatment to evaluate the impact of expectations on the intervention response. Therefore, we included the interaction term between the type of treatment and expectations in a secondary analysis. We also evaluated variables that explained the differences in pain between the two treatments and the relative importance of those variables. Furthermore, patients were asked about their preferred treatment regimen after they had undergone both treatment regimens.

Methods

Trial design

We used a within-subject crossover randomized controlled design that compared third molar extraction on both sides. One side was treated with regular preoperative local anesthetics without hypnosis, and the other side was treated with reduced preoperative local anesthetics and additional hypnosis. The sequence of the treatment and the side of the treatment were both randomized (Barth, Egli, Maier, Meyenberger, & Witt, 2019). The study protocol was registered in the German Clinical Trials Register, DRKS Nr. 00011848.

Participants

Patients were included in the study when they had at least one third molar in the left and right mandible with an indication for extraction by a dentist in an outpatient setting. Patients had to be at least 16 years of age, with a good command of the German language, and were required to use a mobile phone to receive text messages. Patients using illegal drugs, psychotropic drugs or opioids were excluded from the study, as were patients with a diagnosed mental disorder with associated dissociation problems such as schizophrenia, borderline personality disorder or posttraumatic stress disorder.

Sample size

We performed a priori sample size calculations with an assumed effect size of 0.68 between groups in an ANOVA with repeated measures (Barth, Egli, et al., 2019) because of missing data with area under the curve with respect to ground (AUC_G) comparisons. We assumed five time points for the assessment and made different assumptions about the autocorrelation (rho) of pain assessments ranging from 0.5 to 0.85, since the real autocorrelation is unknown. The required sample size to detect the assumed effect with 80% power and an alpha of 5% was 31 (rho = 0.8). We therefore used a sample size of N = 33 to account for an expected two dropouts during the study.

Randomization

To perform a randomized four-armed trial with two independent factors, patients were randomized in a 1:1:1:1 ratio (see Figure 1). The central block randomization had a variable block length. The independent factors were the order of side of the third molar extraction (left/right) and the order of the intervention (third molar extraction with regular preoperative

local anesthetics without hypnosis vs. reduced preoperative local anesthetics and additional hypnosis).

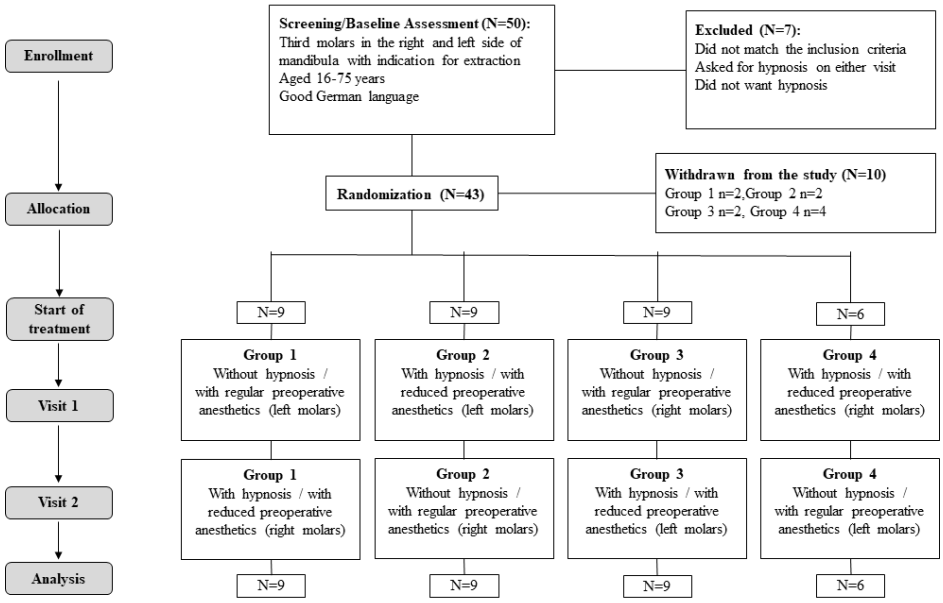

Figure 1: Flow chart of the crossover study design. Each patient was randomly assigned to one of the four groups.

Group 1: Extraction left, regular preoperative local anesthetics without hypnosis (visit 1). Extraction right, reduced preoperative local anesthetics and additional hypnosis (visit 2).

Group 2: Extraction left, reduced preoperative local anesthetics and additional hypnosis (visit 1). Extraction right, regular preoperative local anesthetics without hypnosis (visit 2).

Group 3: Extraction right, regular preoperative local anesthetics without hypnosis (visit 1). Extraction left, reduced preoperative local anesthetics and additional hypnosis (visit 2).

Group 4: Extraction right, reduced preoperative local anesthetics and additional hypnosis (visit 1). Extraction left, regular preoperative local anesthetics without hypnosis (visit 2).

A team member of the Institute for Complementary and Integrative Medicine with no further involvement in the study generated the randomization sequence using R (version 3.1.0). To assure allocation concealment of the patient group, REDCap® (Clinical Trial Center, University Hospital Zürich) was used.

Blinding

It was not possible to blind the dentist or the patient in this study to the intervention. However, we did not specify in advance in the patient information the amount of reduced medication and highlighted as the study aim mainly the research question about the effectiveness of hypnosis. For the statistical analysis, the statistician was blinded. All outcomes were self-report measures completed by the patient or the dentist.

Recruitment and screening

Between February 2017 and August 2018, the recruitment and treatment of patients was performed in the outpatient dental clinic of Dr. Meyenberger in Wil, Switzerland. Every possible study participant was screened by a dentist and informed about the study. If he or she agreed to participate in the study, informed consent was obtained and the patient was randomized. The baseline assessment was performed before the first surgery visit of the patient. The patients received a voucher of 50 Swiss Francs for a service of the dentist if they participated in the study.

Baseline assessment

For the patient's recognition of the effectiveness of hypnosis, the Expectation for Treatment Scale (ETS) was used (Barth, Kern, Lüthi, & Witt, 2019). In four questions about the patients' expectations, the patient could select one of four response options, ranging from low expectations (1 point) to high expectations (4 points). Single items were summarized on a

scale with a minimum score of 4 points (low expectations) and a maximum score of 16 points (high expectations). The internal consistency of the scale was good, with a Cronbach alpha of .865. Additionally, information about previous hypnosis experience and the subjective benefit of hypnosis was collected. Each patient was asked about their preference after both treatments were completed (reduced preoperative local anesthetics and additional hypnosis or regular preoperative local anesthetics without hypnosis).

Dental anxiety was assessed with the German translated Dental Anxiety Scale (DAS) (Tönnies, Mehrstedt, & Eisentraut, 2002), which consists of four items about sweating or the feeling of discomfort with five response options ranging from relaxed (1 point) to anxious (5 points). Higher anxiety corresponds to higher total scores, with values ≥16 points indicating strong dental phobia, 11–15 points indicating slight anxiety and ≤10 points indicating little or no anxiety (Berggren & Meynert, 1984; Corah, Gale, & Illig, 1978; Tönnies et al., 2002). Cronbach's alpha for the DAS was good (α=.857).

Intervention

For hypnosis, we used verbatim induction based on the so-called Dave Elman technique. The following steps are included in this technique: induction, deepening and release. The complete text of the instructions is shown in a protocol published elsewhere (Barth, Egli, et al., 2019). The induction used suggestions for a relaxation response, employed counting for deepening and shifted the attention to a beautiful place. The induction was performed in the dental chair before starting with the surgical procedure, and the mean duration was 7.9 minutes (range 6 to 10).

Molar extraction

The third molars on the right and left side were extracted lege artis (Coulthard et al., 2014; Farish & Bouloux, 2007; Gujer et al., 2013) and in two separate visits. The time between the

surgeries was a minimum of three weeks. We did not perform the second surgery until the patient showed no signs of pain or any discomfort from the first extraction. One extraction was performed with reduced preoperative local anesthetics and additional hypnosis, and the other extraction was performed with regular preoperative local anesthetics without hypnosis (visit 1 or visit 2). To extract the third molars, patients received conductive and/or infiltrative anesthesia with 4% articain with 1:200,000 epinephrine which is the standard medication according to latest evidence (Boonsiriseth et al., 2017; Kim et al., 2018; Yang et al., 2020; Zhang et al., 2019). The amount of anesthesia depended on the treatment. As a regular dose for the treatment without hypnosis, we used 1.7 ml of 4% articain for each third molar (treatment with regular preoperative local anesthetics without hypnosis), and in combination with hypnosis (treatment with reduced preoperative local anesthetics and additional hypnosis), we used half of this dose, i.e., 0.85 ml of 4% articain. Patients received mefenamic acid 500 mg to take at home if needed. Patients could take postoperative systemic analgesics medications after both treatment regimens if needed. Approximately one week after third molar extraction, wound control was conducted.

Outcomes

Primary outcome

To measure the primary outcome (AUC_G of pain intensity after the treatment) a Numeric Rating Scale (NRS) ranging from 0 to 10 was filled in by the patients after visit 1 and visit 2. Higher values indicate more intensive pain (Downie et al., 1978). Pain was assessed in a diary by the patients at five time points, namely, immediately after the treatment, 3 hours after the third molar extraction, in the evening of the molar extraction day, and in the evening of the following two days. Patients received text messages prior to each time point as a reminder to fill in the diary to increase the data quality. The AUC_G of these pain scores was calculated as the primary endpoint (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

AUC_G was used instead of AUC_I because we were more interested in the "total amount of pain" and not that much in peaks of pain over time.

Secondary outcomes

For the secondary outcome (amount of postoperative analgesics and the preferred treatment) the postoperative drug intake had to be listed by the patients in a diary at four time points: three hours after the treatment, on the evening of the treatment and one day and two days after the treatment in the evening. At the last appointment after the third molar extractions had been completed, patients were asked about their preferred third molar extraction intervention (treatment with reduced preoperative local anesthetics and additional hypnosis vs. treatment with regular preoperative local anesthetics without hypnosis).

Additional measures

When hypnosis was used, patients filled in the Inventory Scale of Hypnotic Depth (ISHD) to measure the subjectively perceived hypnotic depth of the Elman induction. ISHD consists of 38 items. Each item had four response options. For 31 items, the patient rated the hypnotic depth on a scale from 1 (not effective) to 4 (very effective), and for the remaining seven items, the patient rated the hypnotic depth on a scale from 1 (very effective) to 4 (not effective). For the latter six items, the scale was inverted to calculate the sum score, which is an indicator of the hypnotic depth (≤ 70 points: slight hypnotic depth; 71–94 points medium hypnotic depth; ≥95 points deep hypnotic depth) (Field, 1965; Riegel, Isernhagen, Torlopp, & Ritterbusch, 2018). The ISHD showed a Cronbach's alpha of .868, which indicates good internal consistency of the scale. For the experienced depth of hypnosis according to the dentist's impression, we used a numeric scale ranging from low experienced depth (0 points) to high experienced depth (10 points). At the second follow-up appointment, the patient was additionally asked about adverse events.

Statistical methods

To determine whether pain differs between treatments, a linear mixed effects model controlling for gender was used. The binary variables treatment regimens (with or without hypnosis) and gender (male/female) were included as fixed effects, and a subject-specific random intercept accounted for the within-patient correlation of pain. Additionally, a sensitivity analysis extended the linear mixed-effects model with the variables visit (first/second) and side (left/right).

To determine the impact of expectations on the effectiveness of hypnosis, the above mentioned linear mixed-effects model was extended with the continuous variable patient's expectations, as well as the interaction of the treatment regimens and the patient's expectations.

To determine which variables explained the differences in pain between the two treatments, the difference between the AUC_G of pain under hypnosis with reduced preoperative local anesthetics minus the AUC_G of pain without hypnosis and regular preoperative local anesthetics was the dependent variable, and gender, patient's expectations, patient-rated hypnotic depth, dentist-rated hypnotic depth and patient's fear of dentists were the independent variables in the linear model. The relative importance of each independent variable was determined by calculating the proportion of the variance in the dependent variable explained by the independent variable (between 0% and 100%). A Wilcoxon rank test was used to investigate whether the amount of pain medication differed between groups.

To examine treatment preferences, the odds that a patient preferred treatment with hypnosis were calculated with logistic regression. All analyses were conducted in R (R Core Team, 2020).

Results

A total of 43 patients were screened for eligibility and randomized. Since 10 patients declined participation before receiving any kind of treatment 33 patients were included in the analysis. We included 19 female patients (57.6%), with a mean age of 25 years (SD = 6.6). German was the first language of 32 patients. Thirty patients indicated not needing to take any medication, 2 patients took contraceptive pills and 1 patient took the medication Concerta (Methylphenidat). The highest completed education of the patients was as follows: 5 patients had a university degree, 7 patients higher vocational training, 13 patients did an apprenticeship or attended a vocational school, 3 patients had an A-level certificate and 10 patients had completed compulsory school.

Before the first treatment, the mean expectations for hypnosis were rather low (mean = 8.33, SD = 2.94, ranging from 4 to 16). However, 26 out of 33 patients had a preference before the treatment for the treatment condition with hypnosis. Dental anxiety was also low (M = 9.30, SD = 3.19, ranging from 5 to 17). Fifteen treatments with reduced preoperative local anesthetics and additional hypnosis needed additional local anesthesia during the tooth extraction, and 11 treatments with regular preoperative local anesthetics without hypnosis needed additional local anesthesia during the tooth extraction. The hypnotic depth on the ISHD was rather high (M = 95.79, SD = 13.91, ranging from 67 to 121), and according to the dentist's observations, the hypnotic depth was high (M = 9.15, SD = 1.46, ranging from 4 to 10).

Effectiveness of hypnosis: The median of the AUC_G for the treatment with reduced preoperative local anesthesia and additional hypnosis was 145.50 and the median of the AUC_G for the treatment with regular preoperative local anesthesia without hypnosis was 94.50. No evidence was found for a difference in the AUC_G of pain between the two treatments when controlling for gender (the estimated AUC_G of pain was 13.36 units higher under treatment with reduced preoperative local anesthetics and additional hypnosis compared

to treatment with regular preoperative local anesthetics without hypnosis; 95% CI from −18.80 to 45.53; p = 0.42). In the sensitivity analysis including gender, visit and side of extraction, the estimated AUC_G of pain changed only slightly (AUC_G of pain was 11.81 units higher under treatment with reduced preoperative local anesthetics and additional hypnosis compared to treatment with regular preoperative local anesthetics without hypnosis), but there was still no evidence for a difference between the treatment conditions. There was weak evidence that AUC_G for pain was higher at the second visit, with an AUC_G difference of 26.44 units (95% CI from –5.43 to 58.32; p = 0.10; see Table 1).

The mean pain score after 1 day was 2.58 (SD 2.14) for the treatment with regular preoperative local anesthetics without hypnosis and 2.88 (SD 1.90) for the treatment with reduced preoperative local anesthetics and additional hypnosis. Means and standard deviations of the pain scores from which the AUC_Gs were calculated are shown in the appendix (Table 1A). Moreover, a table with the estimated coefficients (unstandardized beta) of possible predictors for the differences in the AUC_G of pain between treatments is also in the appendix (Table 2A).

There was no evidence that the amount of pain self-medication by the patients differed between treatment regimens (p-value = 0.34). In both treatments, the median amount of pain medication after surgery was equal to 3.00. Most patients used mefenamic acid, and if other substances were used, only pain medications available by prescription were taken into account for the statistical analysis (see Table 3A in the appendix).

Table 1: Estimated mean difference in the AUC_G of pain after treatment with reduced preoperative local anesthetics and additional hypnosis compared to the treatment with regular preoperative local anesthetics without hypnosis, controlling for gender, visit and side of extraction.

	Estimated coefficients	**95% Confidence interval**	**p-value**
(Intercept)	106.56	65.49 to 147.63	< 0.0001
Treatment with hypnosis	11.81 (mean difference)	-20.07 to 43.68	0.47
Male gender	7.55	-40.40 to 55.50	0.76
Second visit	26.44	-5.43 to 58.32	0.10
Extraction on right side	9.31	-22.57 to 41.18	0.57

There was moderate evidence for an interaction effect between the patients' expectations and the type of treatment (see Table 2, p = 0.021). Figure 2 shows the estimated slopes of the two treatments, indicating that the effectiveness of hypnosis for pain reduction increased with higher patients' expectations of hypnosis. This means that patients with high expectations benefited on average more from treatment with reduced preoperative local anesthetics and additional hypnosis, while patients with low expectations did not benefit from such a treatment. This corresponds with the estimated relative importance of the patient's expectations on the AUC_G pain difference, which was 15.98% and, thus, by far, the largest proportion (see appendix Table 2A). Gender had an estimated relative importance of 5.30%.

There was no evidence that the AUC_G pain difference between the two treatments was influenced by the patient-rated hypnotic depth, the dentist-rated hypnotic depth or the patient's fear of dentists.

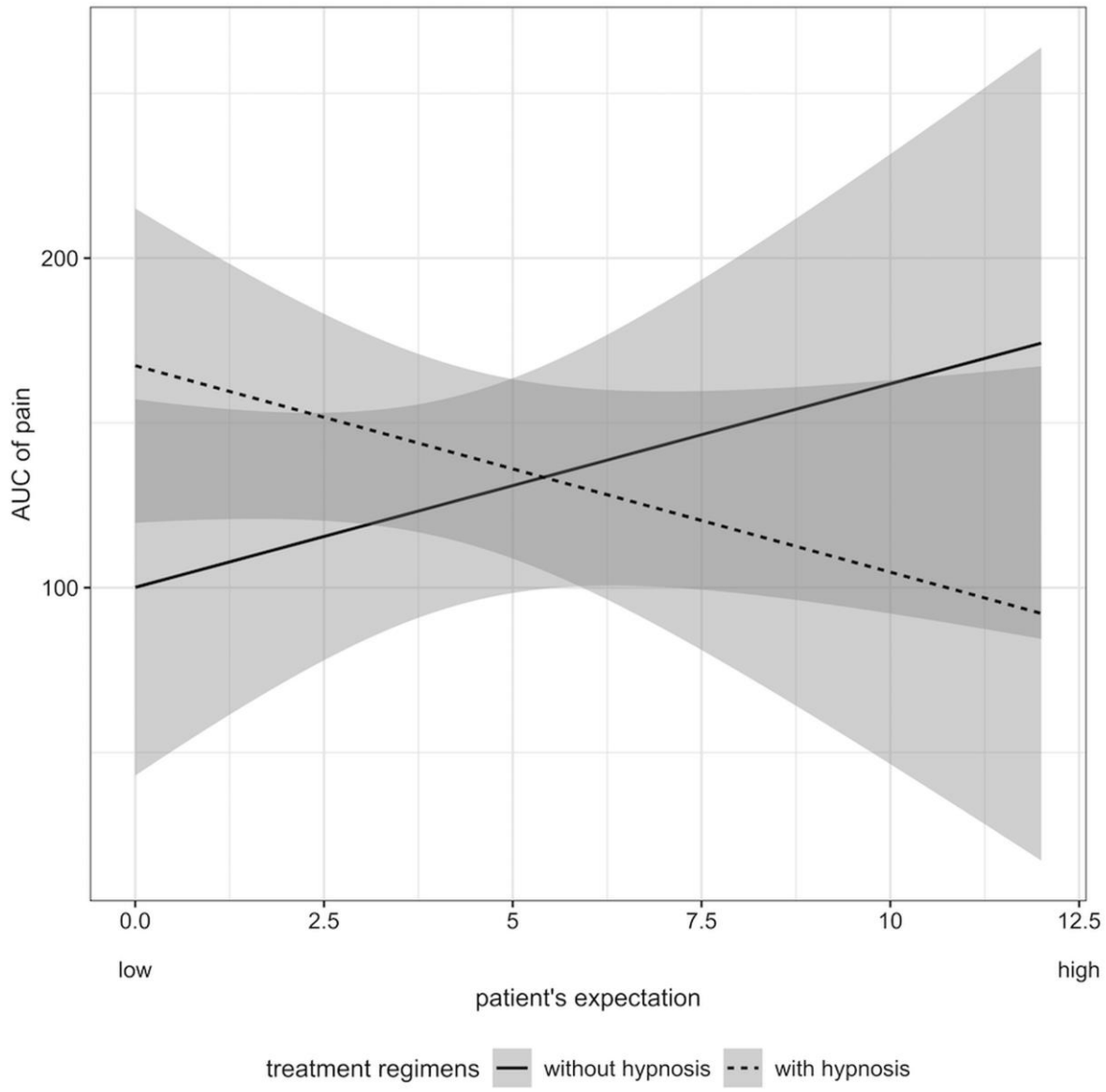

Figure 2: Visualization of the interaction effect of patients' expectations about hypnosis effectiveness, the type of treatment (reduced preoperative local anesthetics and additional hypnosis vs. treatment with regular preoperative local anesthetics without hypnosis) and the amount of pain (AUC_G of pain) ($p = 0.021$). Slopes reflect raw values in both treatment conditions.

Note: The scale of patient expectations was re-scaled for this visualization (original range from 4 to 16; range here from 0 to 12)

Table 2: Estimated mean difference in the AUC_G of pain under treatment with reduced preoperative local anesthetics and additional hypnosis vs. the treatment with regular preoperative local anesthetics without hypnosis, controlling for gender, patient expectations, visits, side and the interaction between treatment regimens and patients' expectations.

	Mean difference	**95% Confidence interval**	**p-value**
(Intercept)	79.84	17.84 to 141.83	0.012
Treatment with hypnosis	64.06	10.49 to 117.64	0.019
Male gender	7.89	-42.14 to 57.93	0.76
Patient expectations	6.25	-3.69 to 16.20	0.22
Second visit	24.15	-5.73 to 54.03	0.11
Extraction on right side	10.27	-19.55 to 40.09	0.50
Interaction term: Treatment with hypnosis by patient's expectation	-11.99	-22.21 to -1.78	0.021

Regarding patients' preferences: 81.8% of the patients preferred treatment with reduced preoperative local anesthetics and additional hypnosis, and 18.2% preferred treatment with regular preoperative local anesthetics without hypnosis. The odds for a treatment preference

with reduced preoperative local anesthetics and additional hypnosis was therefore 4.50 (95% CI from 1.86 to 10.90), indicating very strong evidence for a preference for an extraction with reduced preoperative local anesthetics and additional hypnosis. There was no evidence for a difference in patients' preferred treatment by gender (odds of preferring hypnosis was 1.60 higher for males compared to female patients with a 95% CI from 0.25 to 10.27). There is weak evidence that the patient's preferred treatment regimen depended on the patient's expectations of hypnosis. When the patient's expectations increased by 1 unit, the odds to prefer a treatment under hypnosis increased by a factor of 1.67 with a 95% CI ranging from 0.98 to 2.84. There was also evidence that the patient's preferred treatment regimen depended on the patient-rated hypnotic depth. When the patient-rated hypnotic depth increased by 1 unit, the odds of preferring the treatment with reduced preoperative local anesthetics and additional hypnosis increased by a factor of 1.09 with a 95% CI ranging from 1.00 to 1.18. The Spearman rank correlation coefficient of 0.185 indicates very weak correlation between the variables self-reported hypnotic depth and patient's expectation.

Discussion

Our study revealed no evidence for a difference in the pain intensity by adding a hypnosis intervention to a reduced preoperative local anesthetics treatment in patients during third molar extraction compared to the standard treatment (regular preoperative local anesthetics without hypnosis). However, we found evidence for an interaction of pre-treatment expectations and the type of treatment: patients with high expectations about the effectiveness of hypnosis had greater benefits from the hypnosis intervention with reduced local anesthetics.

Our findings differ from earlier studies that found very large effects of hypnosis on pain during third molar extraction (Venkiteswaran & Tandon, 2021). This difference might be explained by our rigorous trial design, the outcome assessment, the fact that we used a within-subject design and the choice of our intervention using reduced preoperative local anesthetics in the hypnosis condition. Previous studies did not report any details about their randomization procedure (Abdeshahi et al., 2013; Ghoneim et al., 2000; Mackey, 2018; Peimani et al., 2017). Additionally, the outcome assessment was only performed at one specific time point (i.e., 24 hours after tooth extraction) (Mackey, 2009, 2018), and our multiple outcome assessment might be more reliable. Both aspects might contribute to biased effects in earlier works. In our study, we used a within-subject design instead of a comparison between a treatment vs. control group (Enqvist & Fischer, 1997; Ghoneim et al., 2000; Mackey, 2009, 2018); therefore, estimates might be more precise in our study since the individual differences in pain sensitivity are eliminated. Earlier studies used mainly standardized audio instructions (Enqvist et al., 1997; Ghoneim et al., 2000; Mackey, 2009, 2018) which is a difference to our study. Nevertheless, our study also has the limitation as in many earlier studies that the number of treatment providers is low and multicenter studies are not a common practice, which limits the generalizability of our findings.

To our knowledge, this is the first study to provide evidence for the importance of expectations in hypnosis in a within-subject design in an applied context. Such an association has already been stated in theoretical papers "People using hypnosis expect that after entering an altered state they will be more suggestible; that is, the hypnotist will be able to give a suggestion that will profoundly change their perception […]" (Holroyd, 2003). To date, available studies on third molar extraction have not assessed the expectations of patients in advance (Enqvist & Fischer, 1997; Facco et al., 2011; Ghoneim et al., 2000; Mackey, 2009). Our study is in line with other clinical studies showing that patients with high outcome expectations had larger treatment effects on pain compared to patients with lower outcome expectations (Groeneweg et al., 2017; Kalauokalani, Cherkin, Sherman, Koepsell, & Deyo, 2001; Linde et al., 2007; Myers et al., 2008). Expectations are also considered as an important mechanism for a placebo response of (non-specific) pain treatments (Colloca, 2019) which might contribute to the hypnosis effects in our study. Suggestions targeting expectations have been found to decrease pain also in clinical populations (Peerdeman et al., 2016). Despite the fact that our study did not manipulation expectations by specific communication we found evidence for the importance of expectations from an observational study. This finding is also in line with the theory of hypnosis, which assumes that the effects of hypnosis depend on the patients' beliefs about hypnosis (Barber, 1972; Sarbin & Coe, 1972; Spanos, Brett, Menary, & Cross, 1987; Spanos, Gabora, & Hyndford, 1991).

The findings about treatment preferences indicate that, in general, hypnosis might be a valuable additional intervention in the field of tooth extractions. This finding is in line with survey data indicating a high popularity of hypnosis among the general public (Krouwel, Jolly, & Greenfield, 2017; Palsson, Twist, & Walker, 2019). According to our findings, expectations and preferences are not affected by gender, which allows for good generalizability of hypnosis into usual care. Our intervention worked without pre-selection of easily hypnotizable patients. The assessment of patients for hypnotizability is not possible in

routine clinical practice because it is a lengthy procedure. Hypnosis was accessible to most patients in this clinical context (high self-reported and clinician observed hypnotic depth), confirming prior reports that in the clinical setting, hypnosis can be perceived as successful independently of hypnotic susceptibility. Hypnosis may be useful to prepare patients for treatment (i.e., to alleviate dental anxiety) but also adds to the treatment itself. Non-inferiority trials might be needed to compare hypnosis head to head with other treatments that have been proven to be effective.

Limitations

First, our study does not allow for drawing explicit conclusions about the effectiveness of hypnosis as an additive treatment in third molar extraction since we used a reduced amount of anesthesia in the treatments with hypnosis Our study indicate no evidence for a difference in outcomes between a reduced medication treatment and hypnosis compared to normal medication without hypnosis. The decision to use this treatment design was based on earlier trials. Some trials compared hypnosis (without medication) vs. medication (Abdeshahi et al., 2013; Peimani et al., 2017), while others compared medication plus hypnosis vs. medication alone (Ghoneim et al., 2000; Mackey, 2009, 2018). The first type of studies are hard to conduct in our health care system since patients are used to receiving medication. Our study is therefore a combination of both earlier types of studies, and it showed that outcomes are not improved by adding a hypnosis intervention to a reduced anesthetic treatment in patients during third molar extraction compared to the standard treatment. However, we cannot be sure whether using half of the dose lowered the chance for a potential benefit of hypnosis. Second, during the recruitment and information process, patients may not have agreed to participate in the study if they had a strong preference for only one treatment option and did not want to undergo third molar extraction with both types of intervention. Furthermore, 43 patients were randomized in the trial, but only 33 received the intervention and baseline data are available

because the initial assessment was conducted weeks before the first surgery in all patients. However, all patients with a first visit were analyzed according to the intent to treat principle. Since the randomization only changed the side of the intervention and the order of the treatments in our within subject design, this problem can be neglected. Third, in patients with third molars both in the mandible and the maxilla on one side, the extraction was performed at the same visit. As a result, not all patients had to undergo the same extent of surgery. Thirty-one patients had two third molars in the maxilla, and only two patients had one third molar in the maxilla. Fourth, the pre-planned preoperative local anesthetics were not sufficient in 26 of 66 treatments, and additional intraoperative local anesthesia was necessary. Fifteen treatments with reduced preoperative local anesthesia and hypnosis needed additional anesthesia during molar extraction, whereas 11 treatments with regular preoperative local anesthetics without hypnosis needed additional anesthesia during molar extraction. This means that the number of treatments that required additional anesthesia in both treatment conditions was similar. Fifth, the absence of direct suggestions for pain relief in the Dave Elman hypnotic introduction can be regarded as a potential limitation since pain relief suggestions were not used, contrary to the recommendations of earlier work (Milling, Kirsch, Allen, & Reutenauer, 2005). There is, however, a common use of the Dave Elman instructions in this setting, and it can easily be implemented in routine care without prior preparation work of patients to get familiar with suggestions.

Strengths

First, prior to this publication, the study was registered, and the study protocol was published. Therefore, it was not possible to make adaptations to the treatment procedure or analysis procedures afterwards. However, our within-subject design is robust for unbalanced treatment groups since all patients received both treatments, and only the order and side were randomly allocated. We included 33 patients in the within-subject design and each patient was measured

at two molar extractions that took place at different days. Moreover, a within-subject design reduces between-subject error. We believe that a high internal validity of a study is a prerequisite to generalize its findings. Therefore, we tried to conduct a study with a low risk of bias (i.e., high internal validity). The internal validity of our study is therefore excellent. Second, with verbatim induction based on the so-called Dave Elman technique, we used a short, well-defined and standardized hypnotic induction. We aimed to make this induction easy to integrate into the daily routine of an outpatient dental clinic without any prior effort from the patients. A third strength is the high quality of our data (low level of missing data) and the time-dependent assessment of pain over time, which was conducted using SMS reminders on an individual basis.

Conclusions

Third molar extraction from the mandible is a painful treatment, and in this study, hypnosis did not in general help to reduce post-treatment pain. On the other hand, the expectations of the patient about the effectiveness of hypnosis might be a vital prerequisite for the success of hypnosis as an additional treatment in third molar extraction independent of the treatment when reduced preoperative local anesthetics is used. Therefore, hypnosis should be used in patients with high expectations, which might reflect their willingness to become hypnotized. For this purpose, before a treatment with additional hypnosis, a screening instrument could be used by the dentist to identify patients who would respond positively to hypnosis.

Acknowledgments

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Authors' contributions:

Mathias Egli, Jürgen Barth, Stefanie Keiser and Claudia Witt designed the study. Mathias Egli conducted the study and acquired clinical data together with Patrick Meyenberger. Mathias Egli, Jürgen Barth, Manja Deforth and Stefanie Muff analyzed and interpreted data. Mathias Egli prepared the draft of the manuscript. Manja Deforth, Stefanie Keiser, Patrick Meyenberger, Stefanie Muff, Claudia M. Witt and Jürgen Barth revised the manuscript critically for important intellectual content. All authors were involved in the final approval of the version to be published. All authors discussed the results and commented on the manuscript. Mathias Egli and Jürgen Barth take responsibility for the integrity of the work as a whole, from inception to published article.

Study registration and ethics

The study was approved by the respective ethics committee before the start of the study (CEC, Ethikkommission Ostschweiz, BASEC Nr. 2016-02161, 15. February 2017). The study protocol was registered in the German Clinical Trials Register, DRKS Nr. 00011848 on April 11th 2017 and was published in the European Journal of Integrative Medicine (Barth, Egli, et al., 2019). All data were anonymized.

Abdeshahi, S. K., Hashemipour, M. A., Mesgarzadeh, V., Shahidi Payam, A., & Halaj Monfared, A. (2013). Effect of hypnosis on induction of local anaesthesia, pain perception, control of haemorrhage and anxiety during extraction of third molars: a case–control study. *Journal of Cranio-Maxillofacial Surgery*, *41*(4), 310-315. doi:https://doi.org/10.1016/j.jcms.2012.10.009

Al-Shayyab, M. H., & Baqain, Z. H. (2018). Factors predictive of the onset and duration of action of local anesthesia in mandibular third-molar surgery: a prospective study. *European Journal of Oral Sciences*, *126*(2), 110-117. doi:10.1111/eos.12406

Barber, T. (1972). Suggested ("Hypnotic") Behavior: The Trance Paradigm Versus an Alternative Paradigm. Hypnosis: Research Developments and Perspectives (E. Fromm and R. Shor, eds.). In: Aldine Atherton, Inc., Chicago.

Barth, J., Egli, M., Maier, S., Meyenberger, P., & Witt, C. M. (2019). Effectiveness of hypnosis with the Dave Elman technique in third molar extraction: Study protocol for a randomized controlled trial (HypMol). *European Journal of Integrative Medicine*, *26*, 18-23.

Barth, J., Kern, A., Lüthi, S., & Witt, C. M. (2019). Assessment of patients' expectations: development and validation of the Expectation for Treatment Scale (ETS). *BMJ Open*, *9*(6), e026712. doi:10.1136/bmjopen-2018-026712

Benediktsdóttir, I. S., Wenzel, A., Petersen, J. K., & Hintze, H. (2004). Mandibular third molar removal: risk indicators for extended operation time, postoperative pain, and complications. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, *97*(4), 438-446. doi:https://doi.org/10.1016/j.tripleo.2003.10.018

Berggren, U., & Meynert, G. (1984). Dental fear and avoidance: causes, symptoms, and consequences. *Journal of the American Dental Association (1939)*, *109*(2), 247-251.

Boonsiriseth, K., Chaimanakarn, S., Chewpreecha, P., Nonpassopon, N., Khanijou, M., Ping, B., & Wongsirichat, N. (2017). 4% lidocaine versus 4% articaine for inferior alveolar nerve block in impacted lower third molar surgery. *J Dent Anesth Pain Med*, *17*(1), 29-35. doi:10.17245/jdapm.2017.17.1.29

Brown, R. J., Antonova, E., Langley, A., & Oakley, D. A. (2001). The effects of absorption and reduced critical thought on suggestibility in an hypnotic context. *Contemporary Hypnosis*, *18*(2), 62-72. doi:10.1002/ch.220

Burghardt, S., Koranyi, S., Magnucki, G., Strauss, B., & Rosendahl, J. (2018). Non-pharmacological interventions for reducing mental distress in patients undergoing dental procedures: systematic review and meta-analysis. *Journal of Dentistry*, *69*, 22-31. doi:https://doi.org/10.1016/j.jdent.2017.11.005

Castel, A., Pérez, M., Sala, J., Padrol, A., & Rull, M. (2007). Effect of hypnotic suggestion on fibromyalgic pain: comparison between hypnosis and relaxation. *European Journal of Pain*, *11*(4), 463-468.

Colloca, L. (2019). The placebo effect in pain therapies. *Annual review of pharmacology and toxicology*, *59*, 191-211.

Corah, N. L., Gale, E. N., & Illig, S. J. (1978). Assessment of a dental anxiety scale. *Journal of the American Dental Association (1939)*, *97*(5), 816-819.

Coulthard, P., Bailey, E., Esposito, M., Furness, S., Renton, T. F., & Worthington, H. V. (2014). Surgical techniques for the removal of mandibular wisdom teeth. *Cochrane Database of Systematic Reviews*(7). doi:10.1002/14651858.CD004345.pub2

Council, J. R., Kirsch, I., & Hafner, L. P. (1986). Expectancy versus absorption in the prediction of hypnotic responding. *Journal of personality and social psychology*, *50*(1), 182.

Cousineau, D. (2005). Confidence intervals in within-subject designs: A simpler solution to Loftus and Masson's method. *Tutorials in quantitative methods for psychology*, *1*(1), 42-45.

Derbyshire, S. W., Whalley, M. G., & Oakley, D. A. (2009). Fibromyalgia pain and its modulation by hypnotic and non- hypnotic suggestion: An fMRI analysis. *European Journal of Pain, 13*(5), 542-550.

Downie, W., Leatham, P., Rhind, V., Wright, V., Branco, J., & Anderson, J. (1978). Studies with pain rating scales. *Annals of the rheumatic diseases, 37*(4), 378-381.

Enqvist, B., & Fischer, K. (1997). Preoperative hypnotic techniques reduce consumption of analgesics after surgical removal of third mandibular molars: a brief communication. *International Journal of Clinical and Experimental Hypnosis, 45*(2), 102-108.

Facco, E., Casiglia, E., Masiero, S., Tikhonoff, V., Giacomello, M., & Zanette, G. (2011). Effects of hypnotic focused analgesia on dental pain threshold. *International Journal of Clinical and Experimental Hypnosis, 59*(4), 454-468.

Farish, S. E., & Bouloux, G. F. (2007). General technique of third molar removal. *Oral and Maxillofacial Surgery Clinics, 19*(1), 23-43.

Field, P. B. (1965). An inventory scale of hypnotic depth. *International Journal of Clinical and Experimental Hypnosis, 13*(4), 238-249.

Forouzanfar, T., Sabelis, A., Ausems, S., Baart, J., & Van Der Waal, I. (2008). Effect of ice compression on pain after mandibular third molar surgery: a single-blind, randomized controlled trial. *International journal of oral and maxillofacial surgery, 37*(9), 824-830.

Gay, M.-C., Philippot, P., & Luminet, O. (2002). Differential effectiveness of psychological interventions for reducing osteoarthritis pain: a comparison of Erickson hypnosis and Jacobson relaxation. *European Journal of Pain, 6*(1), 1-16.

Ghoneim, M. M., Block, R. I., Sarasin, D. S., Davis, C. S., & Marchman, J. N. (2000). Tape-recorded hypnosis instructions as adjuvant in the care of patients scheduled for third molar surgery. *Anesthesia & Analgesia, 90*(1), 64-68.

Groeneweg, R., Haanstra, T., Bolman, C. A., Oostendorp, R. A., van Tulder, M. W., & Ostelo, R. W. (2017). Treatment success in neck pain: the added predictive value of psychosocial variables in addition to clinical variables. *Scandinavian journal of pain, 14*(1), 44-52.

Gujer, A. K., Jacobsen, C., & Grätz, K. W. (2013). *Facharztwissen Mund-, Kiefer-und Gesichtschirurgie*: Springer-Verlag.

Hammond, D. C. (2008). Hypnosis as sole anesthesia for major surgeries: historical & contemporary perspectives. *American journal of clinical hypnosis, 51*(2), 101-121.

Haug, R. H., Perrott, D. H., Gonzalez, M. L., & Talwar, R. M. (2005). The American Association of Oral and Maxillofacial Surgeons age-related third molar study. *Journal of oral and maxillofacial surgery, 63*(8), 1106-1114.

Holroyd, J. (2003). The science of meditation and the state of hypnosis. *American journal of clinical hypnosis, 46*(2), 118. doi:10.1080/00029157.2003.10403582

Kalauokalani, D., Cherkin, D. C., Sherman, K. J., Koepsell, T. D., & Deyo, R. A. (2001). Lessons from a trial of acupuncture and massage for low back pain: patient expectations and treatment effects. *Spine, 26*(13), 1418-1424.

Kim, C., Hwang, K.-G., & Park, C.-J. (2018). Local anesthesia for mandibular third molar extraction. *Journal of dental anesthesia and pain medicine, 18*(5), 287-294.

Kirsch, I. (1997). Suggestibility or hypnosis: What do our scales really measure? *International Journal of Clinical and Experimental Hypnosis, 45*(3), 212-225.

Krouwel, M., Jolly, K., & Greenfield, S. (2017). What the public think about hypnosis and hypnotherapy: A narrative review of literature covering opinions and attitudes of the general public 1996–2016. *Complementary therapies in medicine, 32*, 75-84.

Lago-Méndez, L., Diniz-Freitas, M., Senra-Rivera, C., Gude-Sampedro, F., Rey, J. M. G., & García-García, A. (2007). Relationships between surgical difficulty and postoperative

pain in lower third molar extractions. *Journal of oral and maxillofacial surgery, 65*(5), 979-983.

Laureano Filho, J. R., de Oliveira e Silva, E. D., Camargo, I. B., & Gouveia, F. M. V. (2005). The influence of cryotherapy on reduction of swelling, pain and trismus after third-molar extraction: A preliminary study. *The Journal of the American Dental Association, 136*(6), 774-778. doi:https://doi.org/10.14219/jada.archive.2005.0261

Linde, K., Witt, C. M., Streng, A., Weidenhammer, W., Wagenpfeil, S., Brinkhaus, B., . . . Melchart, D. (2007). The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain, 128*(3), 264-271.

Mackey, E. F. (2009). Effects of hypnosis as an adjunct to intravenous sedation for third molar extraction: A randomized, blind, controlled study. *Intl. Journal of Clinical and Experimental Hypnosis, 58*(1), 21-38.

Mackey, E. F. (2018). An extension study using hypnotic suggestion as an adjunct to intravenous sedation. *American journal of clinical hypnosis, 60*(4), 378-385.

Mansuri, S., Mujeeb, A., Hussain, S. A., & Hussain, M. A. Z. (2014). Mandibular third molar impactions in male adults: relationship of operative time and types of impaction on inflammatory complications. *Journal of international oral health: JIOH, 6*(2), 9.

Milling, L. S., Kirsch, I., Allen, G. J., & Reutenauer, E. L. (2005). The effects of hypnotic and nonhypnotic imaginative suggestion on pain. *Annals of Behavioral Medicine, 29*(2), 116-127.

Mobilio, N., Vecchiatini, R., Vasquez, M., Calura, G., & Catapano, S. (2017). Effect of flap design and duration of surgery on acute postoperative symptoms and signs after extraction of lower third molars: a randomized prospective study. *Journal of dental research, dental clinics, dental prospects, 11*(3), 156.

Moll, R., Derry, S., Moore, R. A., & McQuay, H. J. (2011). Single dose oral mefenamic acid for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews*(3).

Montgomery, G. H., David, D., Winkel, G., Silverstein, J. H., & Bovbjerg, D. H. (2002). The effectiveness of adjunctive hypnosis with surgical patients: a meta-analysis. *Anesthesia & Analgesia, 94*(6), 1639-1645.

Moore, R. A., Derry, S., Aldington, D., & Wiffen, P. J. (2015). Single dose oral analgesics for acute postoperative pain in adults- an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews*(9).

Myers, S. S., Phillips, R. S., Davis, R. B., Cherkin, D. C., Legedza, A., Kaptchuk, T. J., . . . Connelly, M. T. (2008). Patient expectations as predictors of outcome in patients with acute low back pain. *Journal of general internal medicine, 23*(2), 148-153.

Ostenfeld, T., Price, J., Albanese, M., Bullman, J., Guillard, F., Meyer, I., . . . Nocini, P. F. (2011). A randomized, controlled study to investigate the analgesic efficacy of single doses of the cannabinoid receptor-2 agonist GW842166, ibuprofen or placebo in patients with acute pain following third molar tooth extraction. *The Clinical journal of pain, 27*(8), 668-676.

Palsson, O., Twist, S., & Walker, M. (2019). A national survey of clinical hypnosis views and experiences of the adult population in the United States. *International Journal of Clinical and Experimental Hypnosis, 67*(4), 428-448.

Peerdeman, K. J., van Laarhoven, A. I. M., Keij, S. M., Vase, L., Rovers, M. M., Peters, M. L., & Evers, A. W. M. (2016). Relieving patients' pain with expectation interventions: a meta-analysis. *Pain, 157*(6), 1179-1191. doi:10.1097/j.pain.0000000000000540

Peimani, A., Irannezhad, M., & Ahmadi, A. M. (2017). Comparing the effect of hypnosis and local anesthesia injection on induction of local anesthesia, anxiety, hemorrhage and pain control during tooth extraction. *Journal of Research in Medical and Dental Science, 5*(4), 44-49.

Pekala, R. J., Kumar, V., Maurer, R., Elliott-Carter, N., Moon, E., & Mullen, K. (2010). Suggestibility, expectancy, trance state effects, and hypnotic depth: II. Assessment via the PCI-HAP. *American journal of clinical hypnosis, 52*(4), 291-318.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology, 28*(7), 916-931. doi:10.1016/s0306-4530(02)00108-7

Riegel, B., Isernhagen, J., Torlopp, C., & Ritterbusch, M. (2018). Messung der Trancetiefe mit der deutschen Version der Inventory Scale of Hypnotic Depth. *Verhaltenstherapie, 28*(1), 44-46.

Rowe, N. H., Cudmore, C. L., & Turner, J. L. (1981). Control of pain by mefenamic acid following removal of impacted molar: a double-blind, placebo-controlled study. *Oral Surgery, Oral Medicine, Oral Pathology, 51*(6), 575-580.

R Core Team. (2020). R: A language and environment for statistical computing. R foundation for statistical computing. Vienna, Austria. Retrieved from https://www.R-project.org/

Sarbin, T. R., & Coe, W. C. (1972). *Hypnosis: A social psychological analysis of influence communication*: Holt, Rinehart and Winston.

Sato, F. R. L., Asprino, L., de Araújo, D. E. S., & de Moraes, M. (2009). Short-term outcome of postoperative patient recovery perception after surgical removal of third molars. *Journal of Oral and Maxillofacial Surgery, 67*(5), 1083-1091.

Sierra Rebolledo, A., Delgado Molina, E., Berini Aytés, L., & Gay Escoda, C. (2007). Comparative study of the anesthetic efficacy of 4% articaine versus 2% lidocaine in inferior alveolar nerve block during surgical extraction of impacted lower third molars. *Medicina Oral, Patología Oral y Cirugía Bucal (Internet), 12*(2), 139-144.

Spanos, N. P., Brett, P. J., Menary, E. P., & Cross, W. P. (1987). A measure of attitudes toward hypnosis: Relationships with absorption and hypnotic susceptibility. *American journal of clinical hypnosis, 30*(2), 139-150.

Spanos, N. P., Gabora, N. J., & Hyndford, C. (1991). Expectations and interpretations in hypnotic responding. *Australian Journal of Clinical & Experimental Hypnosis, 19*(2), 87-96.

Tan, G., Rintala, D. H., Jensen, M. P., Fukui, T., Smith, D., & Williams, W. (2015). A randomized controlled trial of hypnosis compared with biofeedback for adults with chronic low back pain. *European Journal of Pain, 19*(2), 271-280.

Tefikow, S., Barth, J., Maichrowitz, S., Beelmann, A., Strauss, B., & Rosendahl, J. (2013). Efficacy of hypnosis in adults undergoing surgery or medical procedures: a meta-analysis of randomized controlled trials. *Clinical Psychology Review, 33*(5), 623-636.

Tönnies, S., Mehrstedt, M., & Eisentraut, I. (2002). Die Dental Anxiety Scale (DAS) und das Dental Fear Survey (DFS) zwei Messinstrumente zur Erfassung von Zahnbehandlungsängsten. *Zeitschrift für Medizinische Psychologie, 11*(2), 63-72.

Venkiteswaran, A., & Tandon, S. (2021). Role of hypnosis in dental treatment: A narrative review. *Journal of International Society of Preventive & Community Dentistry, 11*(2), 115-124. doi:10.4103/jispcd.JISPCD_320_20

Weiser, T., Richter, E., Hegewisch, A., Muse, D., & Lange, R. (2018). Efficacy and safety of a fixed- dose combination of ibuprofen and caffeine in the management of moderate to severe dental pain after third molar extraction. *European Journal of Pain, 22*(1), 28-38.

Weizenhoffer, A., & Hilgard, E. (1959). Stanford hypnotic susceptibility scale, forms a and b. In: Consulting Psychologists Press Palo Alto, Calif.

Wong, S. S. C., Leung, M. Y. Y., & Cheung, C. W. (2019). The effect of total intravenous anaesthesia with propofol on postoperative pain after third molar surgery: A double-blind randomized controlled trial. *European Journal of Pain, 23*(5), 884-893.

Yang, F., Gao, Y., Zhang, L., Zheng, B., Wang, L., Sun, H., & Huang, D. (2020). Local anaesthesia for surgical extraction of mandibular third molars: a systematic review and network meta-analysis. *Clinical Oral Investigations*, *24*(11), 3781-3800.

Zech, N., Hansen, E., Bernardy, K., & Häuser, W. (2017). Efficacy, acceptability and safety of guided imagery/hypnosis in fibromyalgia–A systematic review and meta- analysis of randomized controlled trials. *European Journal of Pain*, *21*(2), 217-227.

Zhang, A., Tang, H., Liu, S., Ma, C., Ma, S., & Zhao, H. (2019). Anesthetic efficiency of articaine versus lidocaine in the extraction of lower third molars: a meta-analysis and systematic review. *Journal of oral and maxillofacial surgery*, *77*(1), 18-28.

Legends:

Figure 1: Flow chart of the crossover study design

Table 1: Estimated mean difference in the AUC_G of pain after treatment with reduced preoperative local anesthetics and additional hypnosis compared to the treatment with regular preoperative local anesthetics without hypnosis, controlling for gender, visit and side of extraction.

Figure 2: Visualization of the interaction effect of patients' expectations about hypnosis effectiveness, the type of treatment (reduced preoperative local anesthetics and additional hypnosis vs. treatment with regular preoperative local anesthetics without hypnosis) and the amount of pain (AUC_G of pain).

Table 2: Estimated difference in the AUC_G of pain under treatment with reduced preoperative local anesthetics and additional hypnosis compared to the treatment with regular preoperative local anesthetics without hypnosis, controlling for gender, patient expectations, visits, side and the interaction between treatment regimens and patients' expectations.

Appendix

Table 1A: Mean pain score (SD) at five different time points after third molar extraction by treatment regimens.

	with reduced preoperative local anesthetics and additional hypnosis	**with regular preoperative local anesthetics without hypnosis**
Number of patients	N=33	N=33
immediately	2.06 (2.09)	1.15 (1.50)
after 3 hours	4.30 (1.96)	3.91 (2.27)
at the evening	4.03 (2.19)	3.36 (2.42)
after 1 day	2.88 (1.90)	2.58 (2.14)
after 2 days	1.79 (1.62)	2.00 (2.05)

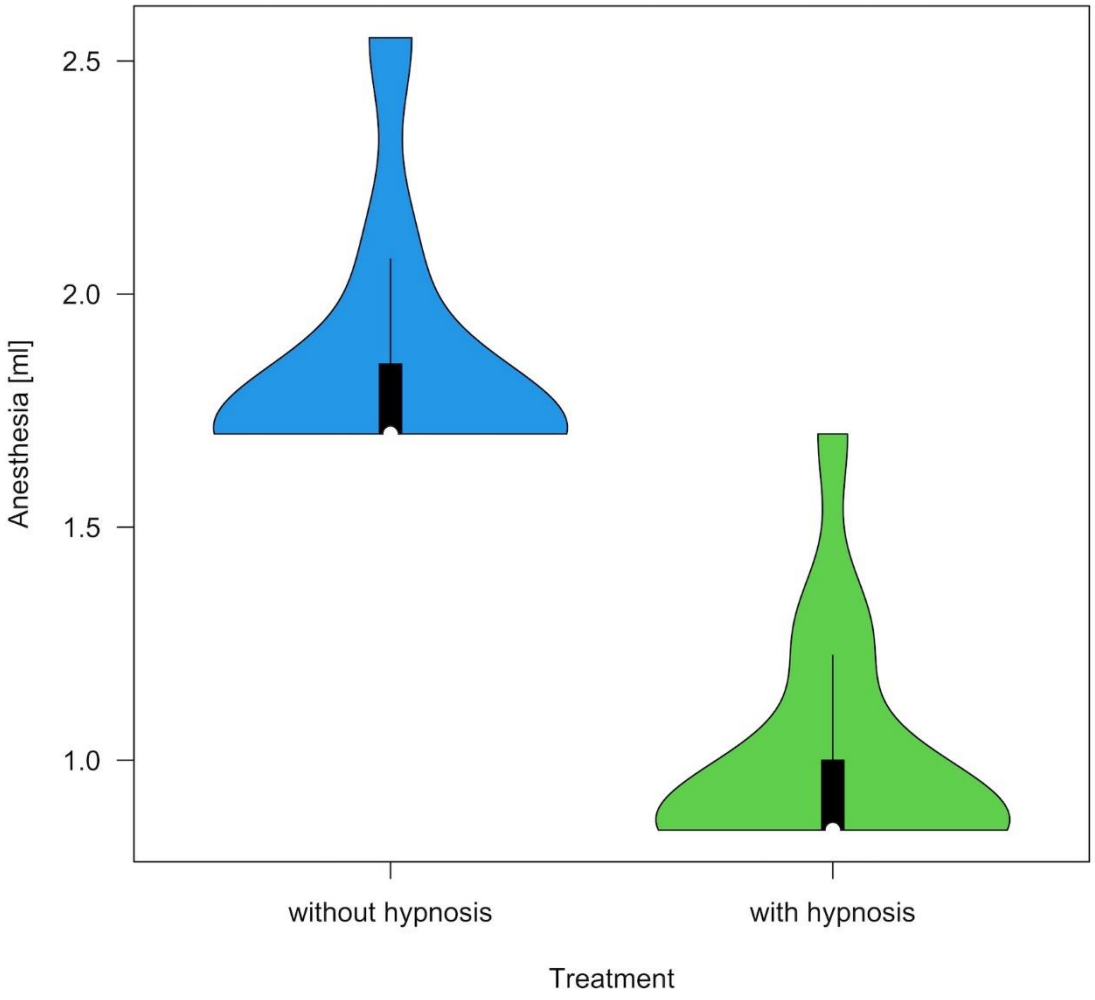
Table 2A: Estimated coefficients (unstandardized beta) and the relative importance of possible predictors for the difference in the AUC_G of pain between treatments. Positive values indicate a positive association between the variable and the difference in the AUC_G of pain between treatments, whereas negative values indicate a negative association.

	Beta	**95% Confidence interval**	**p-value**	**Relative importance [%]**
Intercept	171.41	-39.14 to 381.96	0.12	-
Male gender	-55.98	-123.74 to 11.79	0.12	5.30
Patient's expectation	-14.78	-26.53 to -3.04	0.02	15.98
Patient-rated hypnotic depth	0.33	-2.17 to 2.83	0.80	1.26
Dentist-rated hypnotic depth	-7.69	-29.66 to 14.27	0.50	1.23
Patient's fear of dentists	-2.17	-12.31 to 7.96	0.68	0.99

Table 3A: Overview about the medications (number of pills) taken by treatment regimens.

Medication	with reduced preoperative local anesthetics and additional hypnosis	with regular preoperative local anesthetics without hypnosis
Spiralgin 500 mg	67	82
Co-Amoxicillin Sandozol 1g	0	4
Dafalgan ODIS 500 mg	0	2
Ponstan 500 mg	0	1
Spedifen 600 mg	3	3
Dafalgan 500 mg	1	1
Algifor forte 400 mg	2	0
Spedifen 200 mg	2	0
Arnica cucumbers	1	0
Olfen retard 75 mg	1	0

Figure 1A: Violinplot of the anesthetic treatment in the two treatment conditions, showing the density, median (point and line) and interquartile range (box).



Reviewers' comments:

Reviewer #1:

Review of : Effectiveness of hypnosis in third molar extraction : a randomized controlled trial. JPAIN-D-210040

This study compared the efficacy of using regular local anesthesia in comparison to half-dose local anesthesia + hypnosis on pain perception during and after third molar extraction, in a within-subject and randomized design. The conclusion is that combination of reduced local anesthesia + hypnosis does not provide better relief that regular anesthesia when measured immediately after and up to few days after the extraction. Interestingly, the significant importance of (positive) expectations regarding hypnosis on the reported effect, was confirmed from previous studies - for the first time in a within-subject design.

This is an interesting study that is of importance for the readership of the Journal of Pain.

The study has a very sting design, due to the within-subject format, the randomization and the care to minimize bias. The results are clear and conclusion are in line of the results (of course, one could also conclude that "the use of hypnosis allowed to decrease the amount of local anesthesia used to 50 %...).

The paper is well-written, the methods section is detailed, the discussion is straightforward, and includes the potential limitations of the work.

Response
We thank the reviewer for this positive evaluation of the clinical importance of our paper and the high quality in terms of methodology. This is much appreciated, since we also think that our study moved beyond some shortcomings of earlier studies in this field.

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Reviewer #2:

This manuscript describes a clinical trial examining the efficacy of hypnosis for pain related to third molar extraction. The findings showed no differences between a standard local anesthetic intervention versus hypnosis with reduced local anesthetic dosing. However, expectations regarding the efficacy of hypnosis were associated with reduced pain in the hypnosis condition. These findings are potentially interesting, but several methodological and interpretive issues need to be addressed to more clearly convey the study results.

Comment
1. The authors powered their study based on a fairly large anticipated effects size (0.68). What was the justification for this expected effect size?

Response
We can understand that a effect size of 0.68 rises questions. However, earlier studies showed even much larger effect sizes. Studies with a cross-over design (Abdeshahi et al., 2013 or Peimani et al., 2017) showed effect sizes larger than 1.5 on pain. One of the largest study

(Mackey, 2018), with more than 100 patients, found an effect size on pain of about 1.2. Based on these findings, our assumption can be considered as adequate or even a bit conservative.

Our study included 33 patients in a within-subject design and each patient was measured twice. Since a within-subject design reduces between-subject error, our study had much more power than previous studies.

Abdeshahi, S. K., Hashemipour, M. A., Mesgarzadeh, V., Shahidi Payam, A., & Halaj Monfared, A. (2013). Effect of hypnosis on induction of local anaesthesia, pain perception, control of haemorrhage and anxiety during extraction of third molars: a case–control study. *Journal of Cranio-Maxillofacial Surgery, 41*(4), 310-315. doi:https://doi.org/10.1016/j.jcms.2012.10.009

Mackey, E. F. (2018). An extension study using hypnotic suggestion as an adjunct to intravenous sedation. *American Journal of Clinical Hypnosis, 60*(4), 378-385.

Peimani, A., Irannezhad, M., & Ahmadi, A. M. (2017). Comparing the effect of hypnosis and local anesthesia injection on induction of local anesthesia, anxiety, hemorrhage and pain control during tooth extraction. *Journal of Research in Medical and Dental Science, 5*(4), 44-49.

Comment
2. How were participants recruited for this project? Were incentives offered for participation? This is important as it is plausible that the authors may have enrolled a biased sample, comprised of individuals with a particular affinity for hypnosis, which could influence interpretation of the results.

Response
The patients were recruited within the regular appointments with the dentist before asking for a third molar extraction. A description was already published in the study protocol (Barth et al., 2020 already cited in the manuscript). We have now added that the patients received a voucher for a service of the dentist of CHF 50 (see page 9). This was already mentioned in the study protocol, but we include the information again here because it goes beyond the normal practice

Comment
3. For intention-to-treat analysis, all randomized participants are typically included in the analysis. However, 10 participants withdrew from the project after randomization and were not included in the analysis. Can the authors address this issue? Also, why were these 10 participants withdrawn?

Response
The patients had been initially screened and checked according to the inclusion criteria. When included and randomized, it happened fairly often, due to internal process aspects, that the date of the first surgery was scheduled with a significant time offset after the screening date. This lead to a certain dropout, as some patients changed their mind and withdrew from participation in the study. Practical reasons (patients moved away, time) and preferences (i.e. some patients decided after the screening visit that they wanted hypnosis during both surgerys) were responsible for these withdrawals. Since we do not have any baseline data (beyond eligibility screening data) we have not been able to impute any missing data for those patients. We have already mentioned this problem as limitation (page 21), and we think there is no way to fix this problem, as explained before.

Comment
4. The most significant concern is the constitution of the two intervention conditions. First, the intention was to compare full anesthetic dosing without hypnosis to half dosing plus hypnosis. But, it is conceivable that these two anesthetic doses are similarly efficacious by themselves. The authors should provide some evidence supporting the differences in efficacy of these two doses. Second, a substantial number of individuals required additional anesthetic dosing. How were decisions made requiring additional dosing? And how much additional anesthetic was administered? This issue is important because the administration of additional anesthetic this may have significantly reduced the differences in anesthetic dosing between the groups.

Response
We see that by halving the dose we combined two approaches in one study, which makes it hard to get to a precise estimate for each treatment approach separately. However, we decided this after reflecting options when planning the study. Since there are numerous studies where the effect of hypnosis was added to the effect of an analgesic treatment, a similar study would not have gone beyond the existing knowledge in this field. However, exclusively examining the effect of hypnosis without any analgesic treatment would be not acceptable for ethical reasons. This reasoning was the driver for our study design, which aimed at comparing two treatments that are common practice in Switzerland.

The reviewer asked how the decision was made to individually increase the anesthesic dose and showed concerns as to whether that may have had an impact on the difference between groups in analgesic dosing. Regardless of the group, additional anesthesia was used if a patient experienced and communicated pain during the surgical procedure. The table below shows that there has not been a difference between groups in the amount of additional anesthesia (similar IQR). In our initial submission we had already reported the number of patients receiving additional medication was similar between groups.

Variable	Levels	n	Min	1st quartile	median	mean	3rd quartile	Max	s	IQR
Anesthesia [ml]	without hypnosis	33	1.70	1.70	1.70	1.83	1.85	2.55	0.26	0.15
	with hypnosis	33	0.85	0.85	0.85	0.99	1.00	1.70	0.24	0.15
	all	66	0.85	0.86	1.70	1.41	1.70	2.55	0.49	0.84

Having these findings in mind we see no evidence that halving the dose did negatively affect post-surgical pain per se, but we can not exclude the possibility that the effect of halving the dose was supplemented by a hypnotic effect.
We describe in the manuscript that the high adherence to the study protocol and provide a visual (Figure 1A) showing the dosage for both groups (Violin Plot).

Comment
5. Also, it is surprising that no suggestions for analgesia were included in the hypnosis condition. This seems a likely explanation for the limited effectiveness of the intervention. The authors do little to justify this decision.

Response
We agree that our treatment did not include specific suggestions for pain. However, this is in line with other treatments under the label of “medical hypnosis”, where the aim of the hypnosis is symptom management or the reduction of distress. Our own earlier meta-analysis

(see Tefikow et al., 2013) about hypnosis and surgery showed a lot of variety in instructions and overall, the most often used ingredients are relaxation instructions, distancing from the situation and focusing on breath / visual targets. These features of the hypnostic induction are now mentioned in the manuscript.

> Tefikow S, Barth J, Maichrowitz S, Beelmann A, Strauss B, Rosendahl J. Efficacy of hypnosis in adults undergoing surgery or medical procedures: a meta-analysis of randomized controlled trials. Clin Psychol Rev. 2013 Jul;33(5):623-36. doi: 10.1016/j.cpr.2013.03.005. Epub 2013 Mar 26. PMID: 23628907.

Comment
6. The authors present expectations regarding hypnosis as a potential proxy for hypnotizability. However, this may be better conceptualized as a contributor to placebo responses in the hypnosis group. The authors do not discuss the abundant placebo literature linking patient expectations to their analgesic responses. This requires some attention in the in the Discussion.

Response
We could not agree more that this topic deserves attention. We now have added in the discussion one sentence to highlight the importance of expectations (in the placebo paradigm) for treatment outcomes (in pain) (page 20) which is in line with our findings.

Discussion.
Comment
7. The data presented in Table 4 suggest that pain was generally mild across the 5 time points. This may create something of a floor effect for detecting intervention efficacy. Can the authors address this concern?

Response
The pain levels documented in our study are quite similar to comparable studies and a decline can be expected within the time frame of the follow-up. Since earlier studies with similar courses of pain provide evidence for the effectiveness of hypnosis, it is very unlikely that our findings are affected by a floor effect. Unfortunately, we are not aware of a statistical procedure that can address this issue.

****
Reviewer #3:

The manuscript is very well written and easy to follow. However I am questioned by the relevance of the study, I mean more the relevance of its aims than of its outcomes.

Comment:
I will not extend on the internal validity, which has some limitations, but not so strong that they could alter the interpretation of the data. I would just notice that there was opportunity to reduce the placebo effect by applying a "sham hypnosis" (e.g. neutral and informal conversation). The correlation between expectation and effect you observed is likely to be due to a placebo effect, which was lowered in the control group. Also, the final unbalance between treatments could have added noise and reduced the effect size, if effect there was to be. Personally, I would have used a Latin square to randomise, and anyway would have taken a multiple of four as sample size.

Response

We thank the reviewer for the constructive notes and agree that there had been many different options to set up the study. Using sham hypnosis could be an option and also many other features could be implemented. We abstained from using sham since one single patient have received both types of interventions. Masking the intervention would be very challenging.

The reviewer mentioned the dysbalance of groups. However, we would like to emphasize that the disbalance between groups does not matter that much, since we analyzed the data within one subject (N=33, two treatments). As we can assume that the surgery side and the sequence of hypnosis / no hypnosis does not affect the overall analysis (difference between treatment conditions), the imbalanced number between the allocated groups is not that relevant (confirmed by exploratory analyses).

The reviewer points to an important mechanism of hypnosis (i.e. placebo effect). We have now included this in the discussion to highlight the link of this study to earlier studies about placebo effects in pain treatments. This is very much in line with our understanding of the conceptualization of our study.

Comment

But this is not the main concern. As you have negative results, the first thing to check is statistical power. As the AUC in the control sessions was 127 ± 90, if you wished to identify a 30% decrease (something reasonable), I estimate the post hoc power at 84% with N=33 and an intersession correlation coefficient at 0.5. It would be even better with a better correlation (but I do not find this information in the paper). So the power is good, so the treatment did not work. But here we come to the point: why was there no effect? You cannot be sure, but halving the dose of local anaesthetic could be the reason.

You probably know these pivotal trials of R. Dubner's team (1;2). They evidenced the major usefulness of local/regional anaesthesia, not only to allow the avulsion, but also to prevent postoperative pain. According to what the dentists tell me (I teach anaesthesiology in a dental school), overdosing is not a problem with articaine for third molar extraction. So there is no good reason to reduce the doses, and you may explain that you aimed at being between two extreme conditions (no anaesthesia or "full-dose" anaesthesia), I do not agree because the full-dose is just the mandatory one (and I believe even when there is general anaesthesia, according to Gordon's papers).

This being stated, what is the place for hypnosis? I think it depends on the type of patients. Common patients would have local anaesthesia, the point is actually to know whether hypnosis can add comfort and postoperative analgesia; that was the aim of this study, but I think I explained why it failed. Anxious/phobic patients definitely need additional care, such as conscious sedation with nitrous oxide or midazolam; and in this case hypnosis is an alternative to be tested, given that it needs a different (but more acceptable) training and that it costs time instead of money. In those populations, I guess non-inferiority trials are to be conducted. The issue of the other alternatives (relaxation, music, virtual reality…) and their own advantages and costs has also to be considered.

Reference List

(1) Gordon SM, Dionne RA, Brahim J, Jabir F, Dubner R. Blockade of peripheral neuronal barrage reduces postoperative pain. Pain 1997 Apr;70(2-3):209-15.

(2) Gordon SM, Brahim JS, Dubner R, McCullagh LM, Sang C, Dionne RA. Attenuation of pain in a randomized trial by suppression of peripheral nociceptive activity in the immediate

postoperative period. Anesth Analg 2002 Nov;95(5):1351-7.

Response
The reviewer mentions several aspects we want to address in this response letter and also in the manuscript. We agree that the power of the trial was good, which is supported by the own calculations of the reviewer. The reviewer classifies the study as "no effect" trial, which in fact is in line with our conclusion in the manuscript. Yet, another reviewer emphasized that the intervention is to be considered a success since there has been no difference between the two treatment conditions, even though medication was halved in one of them. It is hard to decide which interpretation of the half dose plus hypnosis intervention could be regarded a success (the fact that it worked as well as the full dose medication versus the rejection of the null hypothesis). We decided to provide very balanced and careful discussion and to describe both treatments as possible options for further investigations and practice.

The author group is well aware of the important papers from Ron Dubner's team. The reviewer raised concerns that the lower dose in the treatment was too low and therefore the additional effect of hypnosis was lower than expected. On the one hand, we agree that 4% articain should be used in the full dose as shown in the network meta-analysis of Yang et al. (2020). On the other hand, we found a similar effectiveness of both treatments if a non-pharmacological treatment (i.e. hypnosis) was combined with a low dose pharmacological treatment (i.e. medication). In addition to that, there are trials using hypnosis without medication and they showed superiority of hypnosis, which supports the idea that hypnosis would work also with low / no medication. Nevertheless, we have now highlighted the limitation that halving the dose might contradict the beneficial effect of hypnosis. We hope, that the reviewer agrees on this procedure.

We fully agree that a non-inferiority trial might be an important next step a) to provide strong evidence of similar effects of different treatments and b) to broaden the training of treatment providers to learn different interventions. We have added this aspect to the discussion to outline its importance (page 20).

Yang, F., Gao, Y., Zhang, L., Zheng, B., Wang, L., Sun, H., & Huang, D. (2020). Local anaesthesia for surgical extraction of mandibular third molars: a systematic review and network meta-analysis. *Clinical Oral Investigations, 24*(11), 3781-3800.

Additional comments:
Comment
* The introduction is very complete but a bit too long (usually, the maximum is 500 words); the details could be moved to the discussion.

Response
There had been very different opinions about the length of the introduction. Some reviewers liked it as it is. Others also asked for an extension (namely expectation and placebo research). We finally decided to keep the introduction as it is and encourage the Editor to give us clear guidance if a shortening or an extension is required.

Comment
* Does the ETS assess the effectiveness of hypnosis, or the efficacy?

Response
Since patients give a response about their belief if hypnosis works for them, in a real world setting the term effectiveness would be most appropriate. We mention in the background the term effectiveness to guide the reader into that direction.

Comment
* Page 13, what is medication Concerta?

Response
This drug corresponds to Methylphenidade and is used to treat attention deficit hyperactivity disorder.

Comment
* Table 1: the mean difference is not the effect size, which is the difference divided by the SD.

Response
We agree and removed the term “effect size”.

Comment
* Discussion: the papers you cite of Ghoneim et al. and Mackey et al. are of major importance in your topic, while they are not described. Furthermore, it seems that the conditions were different between the two studies.

Response
In the second paragraph of the discussion, we did set our results into context to the studies the reviewer mentioned. We have discussed the risk of bias, outcome assessment and delivery of the intervention. However, it would be beyond the scope of a discussion to highlight specific studies. All of them had been mentioned in the introduction and in the discussion.

Comment
* The results in the supplementary table 1 should be given in the Result's chapter (quartiles must be enough).

Response
We removed table 1 as suggested and added the respective information in the results section.

****
Reviewer #4:

Comment
This is a high-quality research study conducted to assess the impact of hypnosis in third molar extraction. The paper is well-written and highly relevant for the readers of the journal. It is rare to find a pre-registered, well documented and well-thought out study about the effectiveness of hypnoanalgesia in a real clinical setting. I really like the study and the manuscript overall. I have a few suggestions below on how the improve the manuscript even further.

Response
We thank the reviewer for this overall very positive statement and the contribution to improve the quality of our manuscript.

Comment
- The study was preregistered in a trial registry. This is stated at the end of the manuscript, but this is highly relevant to evaluate the methods and the findings, so the authors should mention this in the beginning of the methods section as well.

Response
We have added this information at the beginning of the method section.

Comment
- I am happy to see a sample size estimation in the paper. There are some information missing from this section. For example whether this sample size estimation was perfomed a-priori or is this an esitmation that was conducted post-hoc to justify the appropriate sample size. (Due to the trial registry entry I presume this was apriori sample size estimation, but this should be stated in this section as well). Also, the authors note that „We assumed five time points for the assessment and made different assumptions about the autocorrelation (rho) of pain assessments ranging from 0.5 to 0.85, since the real autocorrelation is unknown. The required sample size to detect the assumed effect with 80% power and an alpha of 5% was 31 (rho = 0.8). Lower autocorrleation means more uncertainty and thus, a higher sample size to reach the same power. So it is not clear why the authors chose to use the rho = 0.8 as autocorrelation to choose their sample size target, while they acknowledge
that the autocorrelation could be 0.5 as well, which would have meant a higher sample size. It should be clarified why did the authors choose rho = 0.8 instead of the more conservative rho = 0.5?

Response
We conducted an a priori sample size estimation which was also published in the study protocol.
The correlation between measures is important for the sample size estimation, but it is the opposite direction as the reviewer can see in these calculations. A higher correlation is associated with a larger sample size and vice versa.
If you assume a correlation of 0.8 then the required sample size is larger

F tests – ANOVA: Repeated measures, between factors

Analysis:	A priori: Compute required sample size		
Input:	Effect size f	=	0.34
	α err prob	=	0.05
	Power (1−β err prob)	=	0.80
	Number of groups	=	2
	Number of measurements	=	5
	Corr among rep measures	=	0.8
Output:	Noncentrality parameter λ	=	8.2571429
	Critical F	=	4.0068729
	Numerator df	=	1.0000000
	Denominator df	=	58.0000000
	Total sample size	=	60
	Actual power	=	0.8066680

If you assume a correlation of 0.5 the required sample size is smaller

α err prob	=	0.05
Power (1−β err prob)	=	0.80
Number of groups	=	2
Number of measurements	=	5
Corr among rep measures	=	0.5

Output:	Noncentrality parameter λ	=	8.4773333
	Critical F	=	4.0726538
	Numerator df	=	1.0000000
	Denominator df	=	42.0000000
	Total sample size	=	44
	Actual power	=	0.8117766

The juxtaposition demonstrates that the sample size decreases when the correlation decreases. This can be explained by the fact that a high autocorrelation lowers the treatment effects, because initial values are quite stable over time (i.e. high correlation).

Comment
- Is it possible to share the exact settings of the power analysis software (statistical code or the text description of the G*power settings) to allow for more analytical reproducibility?

Response
Please see the response before.

Comment
- Also, the authors note that „We therefore used a sample size of N = 33 to account for an expected two dropouts during the study." Nevertheless they report that they recruited a total of 43 people (of whome 10 dropped out). This inconsistency should be reconciled in the text. I guess it became apparent that the droput rate will be higher than 2, so they increased the recruitment target, but this should be noted in the text as well.

Response
The target was to have 33 patients to start the first treatment, assuming that if a drop out occurred that would be after the first treatment. However, in our case, some patients refrained from starting the treatment at all. These patients had not been considered in the statistical analysis and were thus not counted as dropout. We now clarified this at the beginning of the results section.

Comment
- Attrition and handling dropouts also needs some more clarity. Why did people drop out? And how was a dropout treated, was a new participant recruited to replace them directly in the group they dropped out of, or was every replacement participant re-randomized?

Response
As stated in the response above, dropout had only happened before a patient started the overall treatment, not during or after the first appointment. The main and only reason for dropout was a change in someone’s decision to undergo the treatment (lack of motivation, etc.). Patients had been randomized according to the pre-defined sequence as described in the paper. Hence, a replacement was neither needed nor foreseen, because such a procedure could have introduced bias itself. Since the randomization has been only relevant for the side and sequence of the procedures it is not that much a problem that patients dropped out before having the first appointment for the first surgical intervention.

Comment
- What does it mean that the statistician was blinded? Was this made possible by masked group names?

Response
Yes, we used masked group names and conducted the analysis with this masked dataset. The statisticians were unblinded once they had completed the analysis.

Comment
- It would be great to see in the paper how were participants informed about the different conditions. Were they for example aware of the reduced dose of analgesic they get in the hypnosis condition? Did they know how much lower the dose was? etc.

Response
We did not specify the reduction of the medication in the written study information and explained in the study's aim mainly the question about the effectiveness of the hypnosis. But we explained verbally that in case of hypnosis a reduced medication will be used. The exact dosage was not part of the description for both treatment conditions. The description of the conditions corresponds to the items we used for the assessment of treatment preferences (regular or reduced medication). It is interesting to see that more than 80% of the patients post hoc preferred the hypnosis plus reduced medication treatment. This can be partly explained by the effect that they were receive any "negative" suggestions about the hypnosis plus reduced medication in advance. We added a short explanation about this in the blinding section since it is related to the issue that patients had not been fully aware of the reduced medication. Since the medication regimen allowed an adaptation of the dose during the surgery this was not an ethical concern.

Comment
- Could the authors also share data about AUC_I, and how would have using AUC_I instead of AUC_G change the conculsion of the analysis?

Response
In the statistical analysis plan we had pre-specified that AUC_G is our outcome, since "total pain" was of interest. AUC_I does reflect more the variability of pain over time which was not the main focus of our research and which was also not reflected in the descriptive data. We would like to abstain from additional exercises, which are not in line with our assumptions.

Comment
- I would like to comment the authors on the clarity of the Statistical mehtods section. It is concide and yet detailed enough.

Response
We thank the reviewer for this positive comment.

Comment
- There was only one thing I did not understand in the analysis plan: „To determine which predictors explained the differences in pain between the two treatments, the difference between the AUC_G of pain under hypnosis with reduced preoperative local anesthetics minus the AUC_G of pain without hypnosis and regular preoperative local anesthetics was the dependent variable, and gender, patient's expectations, patient-rated hypnotic depth, dentist-rated hypnotic depth and patient's fear of dentists were the independent variables in the linear mixed-effects model." - why is this a mixed effect model? If the dependent variable is the difference between the two numbers, then we only have one outcome value for each

participant, so it is not clear what was entered as a random effect term here. This section could use some clarification.

Response
We fully agree with this point. It is a linear model, not a mixed effect mode. We have corrected this in the manuscript.

Comment
- I think the readers should get more information about the recruitment process. I would be especially interested in how was the study „advertised" or presented to potential participants, and how many of the approached people accepted the invitation. This could be important to understand how well this group of people who eventually were included in the analysis represent the population of people who visit the dentist for this procedure. Relatedly, is the dentist's practice specifically known for useing hypnoanalgesia (so do people specifically seek out this dentist because they want to use hypnoanalgesia)? This is especially inportant to getan accurate assessment of the preference results, where people overwhelmingly preferred the hypnosis treatment. But might have this preference already benn there „at baseline"? According to the trial registriy, this data was also recorded. Could the authors provide information on pre-treatment preference as well to put the post-treatment preference in context?

Response
The recruitment took place in the practice of the dentist. This was described in the published study protocol. We have looked as post-treatment preference and more than 80% would prefer the hypnosis treatment. We reported this information already in the manuscript.

Similarly, at baseline 26 out of 33 patients would prefer hypnosis. In the initial submission we mentioned that the expectations were rather low (mean about 8 on a scale from 4 to 16). This indicates that we do not have a pre-selected sample of patients with only high expectations. It is rather the opposite, the trial is despite the elaborate design a very pragmatic study. Nevertheless, the patients would prefer to get hypnosis.

Comment
- Given that the main outcome in this study was post-surgical pain, it is important to know the exact suggestions given in hypnosis. The authors note in the limitations section that there was no direct suggestion for pain relief, but this should be noted earlier, in the description of the intervention, along with other directly relevant information about the suggestions given in the hypnosis intervention. I understand that the hypnosis protocol is published elsewhere, but this is crucial information to understand the results of this particular study.

Response
We have given a very extensive description of the entire wording of the suggestions in the study protocol publication and now mention some key elements in the text of this paper.

The PDF with the description of the intervention is available for free on the journals website and will be available later as in text citation.

Comment
- It is interesting that based on figure 2, the slope of not only the hypnosis condition, but also the without-hypnossi condition seemed to be affected by expectancy. Or are these slopes computed based on the linear model, where these two slopes are naturally connected? It would be good to see the regression line spearately for the hypnosis and non-hypnosis

condition from a simple regression where the only predictor of AUC is expected hypnosis effectiveness. Is there still an effect of expectancy on the non-hypnosis condition AUC? If so this could be discussed. (This could indicate a „hold-back effect", where people who expected hypnosis to be better reported numbers accordingly, to make hypnosis results seem better (this is not necessarily a conscious misinformation, more like a „self-fulfilling prohecy").

Response
The slopes are computed based on the raw values which reflects both treatment conditions. We added this information in the heading of the respective figure.

Comment
- Please, show a figure of average pain ratings at all measurement-points (with error bars if possible) by condition.

Response
We reported these data in the appendix, including also standard deviations. For secondary analysis it is of much help to have such statistics, as provided in the table. We therefore would like to keep the table instead of converting the information into a less meaningful figure.

Comment
Please, provide some references for these statements: „In dentistry, hypnosis is already well established and can be regarded as a valuable addition to the treatment of pain. Hypnosis is therefore not only useful to prepare patients for treatment (i.e., to alleviate dental anxiety) but also adds to the treatment itself. „

Response
We agree that it is disputable since no representative data are available and guidelines differ in their recommendation to use hypnosis in dentistry. We have removed the first sentence to make the statement about the different treatment options more precise (2nd sentence).

Comment
The authors make the claim that „our study showed that outcomes are not worse by reduced medication treatment and hypnosis compared to normal medication without hypnosis." This is not actually true. The results don't provide evidence for equivalence, since the tests you conducted are classical equality tests, which can only give evidence . The authors could supplement their analyses with equivalence tests or bayesian statistics (bayes factor in support of the null hypothesis, or Bayesian ROPE test). Alternatively, they should support their argument with the observed difference in pain between the two conditions and its lack of clinical significance.

Response
We fully agree with this point and have rephrased the respective sentence according to the recommendation of the reviewer and emphasize no significant difference.

Comment
„We included 33 patients in the within-subject design, which at least corresponds to the double sample size (N=66) since each patient was measured twice." - This statement is statistically inaccurate (due to the non-independence between the measurements), and should be deleted or re-formulated.

Response

We have reformulated this sentence and it is now just a pure description of the sample size and the number of measurements (page 22).

Comment
This is also inaccurate: „The number of timepoints of the outcome assessment was made higher by using AUC_G as the primary outcome, which increases the power as well." The number of timepoints are not increased by using AUC.

Response
We agree that AUC does not affect the power of the study since it can be regarded similar to a one time point assessment. Thanks for spotting this inaccurate description. We removed the respective sentence.

Comment
Please share the research data that was analyzed to produce the findings in the paper as a supplementary material or via a data repository such as Open Science Framework or GitHub.

Response
We will share the data on Open Science Framework once the paper is accepted.

Comment
Please, share the analysis code that produces the findings in the paper to improve the analytical reproducibility of the study.

Response
We will share the code on Open Science Framework, once the study is published.

Comment
I think the authors paint a picture that this was a „failed study" to prove the superiority of the hypnosis-based treatment. But the fact that overwhelmingly many people preferred the hypnosis treatment indicates to me that the intervention was a success. Also, the finding that the two conditions were not significantly different even though half of the anaesthetic was used in the hypnosis condition also points to the effectiveness of the approach. So I am a bit surprised that the authors are so reserved about the conclusions.

Response
We tried to phrase it quite balanced in the conclusions. Some reviewer comments suggested to indicate that our study showed “non-inferiority”. However, we tested a superiority hypothesis. So, the other reviewers emphasized that the hypothesis was rejected and therefore it should count as null finding. Having said this, the authors really feel a bit in a trap and decided to be as neutral as we can be. We hope the reviewer is fine with this.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4 to 6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n.a.
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10, 11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11, 12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7, 8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	14 text, no table
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	16 zp 19
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n.a.
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16 to 19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n.a.
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20, 21
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21, 22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	24
Other information			
Registration	23	Registration number and name of trial registry	25
Protocol	24	Where the full trial protocol can be accessed, if available	25
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	n.a.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.